Title: TOWARD A QUANTITATIVE MODEL OF NUCLEOSOME DYNAMICS ALONG GENOMES

We are looking for a motivated postdoctoral researcher to study the *in vivo* dynamic of the nucleosomal array.

Context

Chromatin is a nucleo-protein complex mostly composed of nucleosomes that correspond to the wrapping of about 147 DNA bp around an octamer of histone proteins. By limiting the access of **DNA Binding Proteins (DBPs)** to their cognate genomic sites [Poirier], regional regulation along genome of the nucleosome positioning [Poirier] and amount of wrapped DNA length [Polach], act as a main layer of regulation of genome accessibility. In the last decades, it has been possible to obtain the genome-wide distribution of nucleosome positions in different organisms, different cell types or environmental conditions [Lee,Kaplan, Oberbeckmann, Nocetti, Weiner, Lai]. Strikingly, these distributions revealed a nonrandom organization with alternation of (i) Nucleosome Depleted Regions (NDRs) of typical size <200 bp, flanked by (ii) Nucleosome Periodic Region (NPRs) with well-defined nucleosomal repeat length (NRLs) and (iii) Extended disordered or fuzzy Regions [Chevereau]. In most species, regulatory sites like gene promoters or origins of replication are associated NDRs [Lee, Chevereau] in a cell-type specific manner.

In that context, we and other groups [Chevereau, Chereji] developed thermodynamical models to derive the equilibrium distribution of nucleosomes along genomes. The array of nucleosomes is modeled by a "Tonks-Takahashi" gas, ie a unidimensional fluid of hard spheres (the histone octamers) of fixed size with nearest-neighbor (NN) interactions and sequence-specific binding potentials [Chevereau]. Using analytical formula or transfer-matrix-like methods [Chevereau, Teif2009,2010], such simple models explain qualitatively most of the features observed in experiments: NDR emerge from barriers in hard-sphere binding and NPRs from non-local entropic effects due to the confinement of hard-rods closed to a barrier at high density [Chevereau, Chereji]. Quantitatively, these models predict remarkably well the nucleosome positioning for low-density *in vitro* reconstitution experiments on the yeast genome [Chevereau] and emphasized the key role played by sequence-specificity [Tillo]. However, confronted to the high-density nucleosome distribution extracted from *in vivo* chromatin, local discrepancies are observed, suggesting that the "intrinsic" contribution from sequence-dependent DNA elasticity may not be the only determinant *in vivo*. The sequence-encoded nucleosome positioning might actually constitute a basal ground state that may be "remodeled" *in vivo* by site-specific and histone-mark-associated recruitment and action of trans-acting factors to establish an adapted nucleosome pattern, either permissive or repressive to transcription, replication, ...

In that context, we showed that human as well as all analyzed vertebrate genomes are characterized by the ubiquitous presence of sequence-encoded NDRs, positioning 2-3 compact nucleosomes (NRL~153bp) at each border [Drillon, Brunet]. These 1 kb-sized regions of intrinsic nucleosome positioning covering more than 1/3 of the human genome, are equally found in early and late replicating regions, in intergenic and genic regions but not at gene promoters. Analyses of mutation rate at these loci suggest that these nucleosome positioning motifs are under selection. One possible scenario is that these widely distributed chromatin patterns have been selected in human to favor a fast dynamic of the nucleosomal array, possibly related to histone turnover, nucleosome breathing and remodelling, with consequence for the epigenetic regulation of nuclear functions in a cell-type-specific manner.

Mission: To properly decipher the different *cis* and *trans* contributions to the control of nucleosome positioning and genome accessibility, the **project aim at developing an extended/refined nucleosome positioning model** in order to take into account: (i) the sequence-dependent nucleosomal DNA breathing [Culkin,Möbius,Teif], (ii) the competition with DNA binding proteins, (iii) the out of equilibrium activity of ATP-consuming remodeling factors [Clapier] and (iv) the dynamics of histone variant insertion [Talbert]. One application will be to question

the possible role of vertebrate sequence-encoded NDRs in the nucleosomal array dynamic, nucleosome breathing and histone turnover.

The successful researcher will join the Laboratoire de Physique de l'ENS de Lyon (LPENSL, CNRS UMR5672, project supervisor: C. Vaillant).

Activity: He/she will develop a research activity at the interface between physics and biology, investigating the usage of computational physics for modeling the dynamics of nucleosome positioning and making quantitative predictions that will be tested experimentally by collaborators. By developing kinetic Monte Carlo simulations using the Gillespie scheme [Gillespie], he/she will simulate stochastic dynamics of nucleosomal arrays along genomes: time-evolution of nucleosomes positions and wrapping length as well as time evolution of genome accessibility. He/she will simulate the relaxation dynamics of the nucleosomal array when subject to external perturbation toward its stationary / equilibrium state obtained by the equilibrium approaches that we already developed (see above). To complete the model, we will then introduce the dynamics of histone variants insertion in the kinetic Monte Carlo simulations: Histone variant insertions and eviction will be controlled by kinetic on/off rates that may depend on the genomic positions due (1) to sequence-dependent adsorption energy of the histone variant (that may differ from the canonical one) and (2) to the site-specific recruitment of specialized histone chaperones (sequence dependent modulation of the local chemical potential). As above, we will derive the time-evolution of nucleosomal array organization along with the time evolution of histone variant insertion distribution. For extracting the parameters of the model (on/off rates), he/she will develop inference scheme s from the comparison of the simulations with experimental epigenomic data (nucleosome positioning, accessibility, chip-seq for TFs, Chaperones, Histone variants…) obtained by collaborators or other groups.

Knowhow: The candidate should have have skills in some of the following areas: Statistical & Computatinal Physics, Bipphysics, Data science. Demonstrated interest for biology and genomics. Knowledge of chromatin and nucleosome dynamics will be appreciated. Willingness to work in an interdisciplinary context.

Work context: The researcher will be part of the project funded by Agence National de la Recherche (ANR “CHROMAGNON”, scientific coordinator: B. Audit) on "Chromatin and Genome evolution”. It is a collaborative project between the host team at LPENSL (Benjamin Audit, Cédric Vaillant), the IGFL-EVOL team (IGFL, ENS Lyon, CNRS, project supervisor and team leader: JN Volff) and the IGFL-EPIG team (IGFL, ENS Lyon, CNRS, project supervisor and team leader: Kiran Padmanabhan). The researcher will benefit from the rich and stimulating scientific environment of ENS de Lyon, including the access to the knowhow and computing resources of Centre Blaise Pascal (CBP) and Pôle Scientifique de Modélisation Numérique of ENS de Lyon (PSMN) ().

Communication: Further inquiry should be send to Cédric Vaillant (cedric.vaillant@ens-lyon.fr).

Remuneration: Monthly gross salary will range from 2600 to 4000 euros depending on experience

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